REMARKS

Reconsideration and allowance are requested.

Claims 22-41 are pending. Here, Applicants' examples show that (1) the cell culture support is not a mixture of a polymer and collagen and (2) detaching cultured cancer cells from cell culture support does not require treatment with either a proteolytic enzyme or EGTA.

Information Disclosure Statement

To satisfy their continuing duties of candor and good faith, Applicants bring to the Examiner's attention the following related applications having Serial Nos. 10/333,468, 10/333,473, 10/544,541, 10/544,542, 10/546,275, 10/567,728, 11/587,427, 11/885,222 and 11/885,246. He is invited to consider their prosecution histories and prior art, which are accessible through the PTO's Image File Wrapper (IFW), in view of the Federal Circuit's holding in *McKesson Information Solutions v. Bridge Medical*, 82 USPQ2d 1865 (Fed. Cir. 2007). To avoid duplication of those materials in the PTO's records, reference to the IFW is encouraged but Applicants would be ready to submit copies of these materials for the Examiner's review if he prefers.

Consideration of the Information Disclosure Statement filed July 12, 2010 is also requested.

35 U.S.C. 112 – Written Description

Claims 1, 3, 5-16, 21-24 and 26 were rejected under Section 112, first paragraph, as allegedly failing to comply with the written description requirement. Although they disagree with the Examiner's allegations, Applicants moot this rejection by cancellation of claims 1, 14 and 16 (and their dependent claims) solely to advance prosecution in this application.

Neither of the two challenged limitations (i.e., "polymer having a lower critical temperature for dissolution" in claim 1 and "which has a tumor formed from the sheet of cancer cells, and evaluating the effect of the administered test substance based on increase or decrease in the volume and/or weight of the tumor" in claims 14 and 16) is recited in the pending claims. Therefore, it is improper to reject claims 22-24 and 26.

Withdrawal of the written description rejection made under Section 112, first paragraph, is requested.

35 U.S.C. 112 – Enablement

The Patent Office has the initial burden to question the enablement provided for the claimed invention. M.P.E.P. § 2164.04, and the cases cited therein. It is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. *In re Marzocchi*, 169 USPQ 367, 370 (C.C.P.A. 1971). Specific technical reasons are always required. See M.P.E.P. § 2164.04.

Claims 1, 3, 5-16, 21-24 and 26 were rejected under Section 112, first paragraph, because allegedly the specification "does not reasonably provide enablement for any polymer that changes its hydration force as broadly claimed." Applicants traverse. The teachings in their specification enable the skilled artisan to practice the invention using polymers other than poly(N-isopropylacrylamide) and animals other than nude mice, which are consistent with the scope of the pending claims.

Applicants disclose polymers other than poly(N-isopropylacrylamide) and teach their use in the claimed invention. If the claims are limited to poly(N-isopropylacrylamide), an infringer guided by the present specification could easily practice Applicants' invention using a polymer other than poly(N-isopropylacrylamide) or an animal other than a nude mouse. Thus, the Examiner's proposed limitation of Applicants' claimed invention would be extremely undue. Such a situation is extremely disadvantageous to the Applicants who have disclosed their invention in satisfaction of Section 112, first paragraph.

The Examiner maintains that the present specification does not teach how to use an animal that rejects the cancer cells of the claimed invention. He also insists that the only means for maintaining human cancer cells in an animal is if the animal is immunocompromised, the only immunocompromised animal described by Applicants is a nude mouse, and their specification does not teach how to use an animal that rejects the cancer cells.

But the cancer cells used in the claimed invention are not limited to those derived from a human being. It is taught in the present specification, "The cells to be used in the invention can be derived from various sources that include but are by no means limited to human being, dog, cat, rabbit, rat, swine and sheep" (paragraph [0014]). In other words, the claimed invention encompasses cancer cells obtained from an animal that are transplanted into an animal of the same species (e.g., the case where cancer cells derived from a rat are transplanted into a rat that is immunocompetent).

The Examiner contends that if the animal is not immunocompromised, the cancer cells will be attacked by the host immune system, destroyed, and fail to create a tumor. But if a donor animal from which cancer cells are derived and a host animal into which the cancer cells are transplanted are of the same species, the transplant is not strongly rejected as appears to be known to the Examiner who refers to the case where the former animal and the latter animal are of different species. Thus, if donor animal and host animal are of the same species, a transplanted cancer cell sheet adheres to the body site at which the sheet has been transplanted (see paragraph [0007]). In addition, the size and/or shape of the transplanted tissue can be controlled by preparing a sheet of the cancer cells in a specified size and/or shape (see paragraph [0007]).

An object of Applicants' claimed invention is to provide a non-human animal free from the problems of the prior art (see paragraph [0004]). Thus, once a novel and non-obvious sheet of cancer cells is provided, conventional techniques may be used to select a non-human animal to receive the transplant, where the sheet will survive until selection of an anti-tumor agent. Limitation of the non-human animal to a nude mouse is unjustified.

Similarly, the non-human animal made by Applicants' claimed invention could be used in selecting of an anti-tumor agent without undue experimentation. It was alleged in the Office Action that "specific steps of administering agents, the controls or how to compare the results so that agents that treat cancer are identified" would require undue experimentation. Such techniques would be known to the skilled artisan. Therefore, if this rejection is maintained, the Examiner is respectfully requested to cite evidence or reasoning that the skilled artisan could not utilize conventional techniques to select anti-tumor agents using the novel non-human animal of Applicants' invention.

Withdrawal of the enablement rejection made under Section 112, first paragraph, is requested because it would not require undue experimentation for a person of skill in the art to make and use the claimed invention.

35 U.S.C. 112 – Definiteness

Claims 1, 3, 5-16, 21-24 and 26 were rejected under Section 112, second paragraph, as allegedly "indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." Although they disagree with the Examiner's allegations, Applicants moot this rejection by cancellation of claims 1, 14 and 16 (and their dependent claims) solely to advance prosecution in this application.

None of the challenged limitations is recited in the pending claims. Therefore, it is improper to reject claims 22-24 and 26.

Applicants request withdrawal of the Section 112, second paragraph, rejection because the pending claims are clear and definite.

35 U.S.C. 102 – Novelty

A claim is anticipated only if each and every limitation as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of Calif.*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). The identical invention must be shown in as complete detail as is claimed. See *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989).

Claims 1, 4-7, 9 and 12-13 were rejected under Section 102(b) as allegedly anticipated by Koezuka (Nippon Nogei Kagaku Kaishi, 68:783-792, 1994). Applicants traverse.

Koezuka describes a method for culturing human cancer cells by using a thermo-responsive polymer (PNIPAAm), as well as a substrate conjugated collagen and this polymer. Koezuka's substrate (i.e., a mixture of **collagen** and PNIPAAm) corresponds to the cell culture support of Applicants' invention. In other words, Koezuka's substrate is a PNIPAAm-collagen substrate, which is different from the cell culture support used in Applicants' process. According to Koezuka, the PNIPAAm-collagen substrate is changed from a solid phase to a liquid phase by changing the temperature, and this

change detaches cultured cells for recovery. Moreover, Koezuka's disclosure suggests that the human cancer cell lines are cultured in a gel. In contrast, Applicants' cell culture support as used in the presently claimed process never changes to a liquid phase.

Finally, according to Koezuka's method, **EGTA** is indispensable for detachment of cultured cancer cells from the substrate without using a proteolytic enzyme such as trypsin. But EGTA is not required to practice Applicants' claimed invention.

Withdrawal of the Section 102 rejection is requested because the cited document fails to disclose all limitations of the claimed invention.

35 U.S.C. 103 – Nonobviousness

A claimed invention is unpatentable if the differences between it and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art. *In re Kahn*, 78 USPQ2d 1329, 1334 (Fed. Cir. 2006) citing *Graham v. John Deere*, 148 USPQ 459 (1966). The *Graham* analysis needs to be made explicitly. *KSR Int'l v. Teleflex*, 82 USPQ2d 1385, 1396 (2007). It requires findings of fact and a rational basis for combining the prior art disclosures to produce the claimed invention. See id. ("Often, it will be necessary for a court to look to interrelated teachings of multiple patents . . . and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue"). The use of hindsight reasoning is impermissible. See id. At 1397 ("A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon ex post reasoning"). Thus, a prima facie case of obviousness requires "some rationale, articulation, or reasoned basis to explain why the conclusion of obviousness is correct." *Kahn* at 1335; see *KSR* at 1396. An inquiry should be made as to "whether the improvement is more than the predictable use of prior art elements according to their established functions." Id. But a claim that is directed to a combination of prior art elements "is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." Id. Finally, a determination of prima facie obviousness requires a reasonable expectation of success. See *In re Rinehart*, 189 USPQ 143, 148 (C.C.P.A. 1976).

Claims 1, 3, 5-13, 15-16, 21-24 and 26 were rejected under Section 103(a) as allegedly unpatentable over Koezuka (Nippon Nogei Kagaku Kaishi, 68:783-792, 1994) in view of Sakai (JP 05/192138). Applicants traverse.

As explained above, firstly, a mixture of PNIPAAm and collagen or a PNIPAAm-collagen substrate and, secondly, EGTA are indispensable for Koezuka's method. But Applicants' claimed invention specifically excludes those requirements of Koezuka.

Sakai describes a method of cultivating skin cells comprising: preparing a cell culture support which has a surface of its base coated with a polymer having an upper or lower critical temperature for dissolution in water in a range of 0-80°C, cultivating skin cells on the cell culture support at a temperature not higher than the upper critical temperature for dissolution or at a temperature not lower than the lower critical temperature for dissolution, and thereafter adjusting the temperature to above the upper critical temperature for dissolution or below the lower critical temperature for dissolution, whereby the cultured skin cells are detached.

Sakai teaches, however, that this method is applied only to skin cells. It neither discloses nor suggests that the method can be applied to other normal types of cell or any kind of cancer cell. Moreover, Sakai does not make obvious that when detached cells are in the form of a sheet, they are optionally brought into intimate contact with a carrier at the time the cultivation is completed and the cancer cells can be detached intact from a culture support together with the carrier.

With regard to common general knowledge in the art as of March 4, 2004 (i.e., the filing date of the priority application), only the following cancer cell-transplanted animals were known (see paragraph [0003] of the specification):

1) knockout mice deprived of anti-oncogenes such as APC and p53, and

2) animals in which cancer has been developed by various methods such as the use of chemicals and other carcinogenic agents and direct transplantation of cancer cells of interest.

But use of these animals raised the following problems (see paragraphs [0003] and [0004] of the specification). Among these animals, anti-oncogene knockout mice require fairly sophisticated (and expensive) genetic manipulation. Cancer development with carcinogenic agents requires a prolonged time to accomplish. Transplanting cancer

cells has the advantage of giving experimental results in a short period of time. On the other hand, in the prior art, the transplanted cancer cells have poor "take" and the size and weight of the transplanted cancer tissue vary so greatly from one animal to another that evaluation of various anti-cancer agents involves difficulty in revealing any significant differences in their efficacy. Reasons for this defect include the poor "take" of the transplanted cancer cells and the leakage of the cancer cells suspension from the site of transplantation. Therefore, Applicants believed it was desirable to improve functions of the cells to be transplanted.

The present invention was made to solve the foregoing drawbacks. As stated in paragraph [0015] of the specification, Applicants' present invention is characterized by the following features.

If cells are cultivated on a cell culture support coated on a surface with a polymer (the hydration force of which changes in a temperature range of 0-80°C), the cultivated cells can be detached from the support without a proteolytic enzyme (e.g., trypsin) being used. Only a simple change in the cultivation temperature is required. As a result, the detached cell sheet is free from damage it would have received if treated with a proteolytic enzyme such as trypsin. Since detachment of the cultured cancer cells involves no enzyme treatment, the adherent protein remains intact, assuring good "take" after transplantation. If the cancer cells are in a sheet form, there is another advantage in that the leakage of a cell suspension from the site of transplantation is effectively suppressed to allow for efficient preparation of a cancer cell-transplanted animal.

As illustrated in Examples 1 and 2 of Applicants' specification, their invention has made it possible to form cancer tissue in a cancer cell-transplanted animal in a manner superior to the prior art. None of the documents cited thus far taught or made obvious such an advantageous technique that efficiently produces a cancer cell-transplanted animal by directing attention to the properties of the cells recovered without proteolytic enzyme or EGTA treatment.

The present invention has made it possible to obtain a non-human animal model in which size and/or shape of cancer tissue in the animal can be controlled by preparing a sheet of the cancer cells in a specified size and/or shape. Neither Koezuka nor Sakai would have made the claimed process obvious at the time Applicants' invention was

made. In conclusion, the present invention would not have been obvious with a reasonable expectation of success by even a skilled artisan from the combination of Koezuka and Sakai.

Withdrawal of the Section 103 rejection is requested because the claims would not have been obvious to one of ordinary skill in the art when this invention was made.

Conclusion

Having fully responded to the pending Office Action, Applicants submit that the claims are in condition for allowance and earnestly solicit an early Notice to that effect. The Examiner is invited to contact the undersigned if additional information is required.

Respectfully submitted,

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